

REMARKS

It has come to our attention that an error is found in the relaxin-3 b-chain amino acid sequence represented by SEQ ID NO:3 in the Substitute Sequence Listing submitted June 14, 2006. A "Ser" residue at position 25 has inadvertently been omitted from this sequence. The enclosed second Substitute Sequence Listing corrects this omission by insertion of the missing "Ser at position 25 of SEQ ID NO:3.

Support for this correction may be found in prior art publicly available as of the June 20, 2003 priority date, copies of which are enclosed for the convenience of the Examiner. Relevant pages from PCT published application WO 03/030930 contain reference to relaxin H3 B chain as SEQ ID NO:2 on page 4, lines 10-16; page 5, lines 4-10; pages 5, line 31, through page 6, line 6; page 16, lines 1-7; page 17, lines 19-25; page 19, lines 1-5; page 20, lines 1-7; Fig. 1A, "B Chain"; Fig. 2A, "B Chain Aligns", "Human 3"; and "SEQUENCE LISTING", page 1/6, "H3-B chain", SEQ ID NO:2, where the "Ser" residue at position 25 is present.

In addition, copies of GenBank Accession No. Q8WXF3 and the corresponding entries from the UniProt/Swiss-Prot database showing sequence submission before the June 20, 2003 priority date are included. The GenBank entry also describes the region of the relaxin 3 preproprotein from amino acid positions 26-52 as "processed active peptide" and the "FEATURE" section of the UniProtKB Entry Q8WXF3 includes a "PEPTIDE" described as "Relaxin-3 B chain", each with the "Ser" at position 25 in agreement with the amino acid sequence of the corrected version of SEQ ID NO:3.

This amendment is accompanied by a floppy disk containing the above named sequences, SEQ ID NOS:1-25, in computer readable form, and a paper copy of the sequence information that has been printed from the floppy disk.

The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy. This amendment contains no new matter.

Appl. No. 10/561,304

PATENT

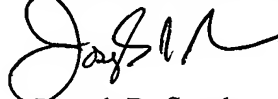
Amdt. dated March 19, 2007

Reply to Notification of Missing Requirements of March 16, 2006

Supplemental Preliminary Amendment

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'J. Snyder', written over the typed name.

Joseph R. Snyder

Reg. No. 39,381

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Attachments

JRS:dmw

60999674 v1

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
17 April 2003 (17.04.2003)

PCT

(10) International Publication Number
WO 03/030930 A1

(51) International Patent Classification⁷: **A61K 38/22**

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(21) International Application Number: PCT/AU02/01338

(22) International Filing Date: 2 October 2002 (02.10.2002)

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PR 8144 8 October 2001 (08.10.2001) AU

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

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(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

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Published:

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: HUMAN 3 RELAXIN

(57) Abstract: Human H3 preprorelaxin, human H3 prorelaxin, human H3 relaxin, human relaxin analogues having a modified A chain and/or a modified B chain are described. Also described are nucleic acid sequences encoded human H3 preprorelaxin, human H3 prorelaxin, human H3 relaxin, human relaxin analogues. Also described are methods for the treatment of conditions responsive to administration of H3 relaxin or analogues thereof.



WO 03/030930 A1

- 4 -

Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser
 1 5 10 15

5 Lys Ser Glu Ile Ser Ser Leu Cys
 20

(SEQ ID NO: 4)

or an amino acid sequence truncated by up to about 9 amino acids from N-terminus,

10 the B chain having the amino sequence:

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
 1 5 10 15

15 Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp
 20 25

(SEQ ID NO: 2)

or an amino acid sequence truncated by up to 9 amino acids from the amino-terminus
 and/or up to about 5 amino acids from the carboxyl-terminus,

20

the A and B chains being linked by interchain disulphide bonds at A11-B10, and A24-B22,
 and wherein the human H3 relaxin or analogue thereof has relaxin bioactivity.

In a third aspect of the invention there is provided a composition comprising a human H3
 25 relaxin analogue having a modified A chain and/or a modified B chain,

the H3 relaxin A chain having the amino acid sequence:

30 Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser
 1 5 10 15

Lys Ser Glu Ile Ser Ser Leu Cys
 20

(SEQ ID NO: 4)

- 5 -

wherein the carboxyl-terminus is an amide derivative and/or Lys at position 12 is replaced with Glu, and/or Glu at position 19 is replaced with Gln,

the H3 relaxin B chain having the amino acid sequence:

5
 Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
 1 5 10 15
 Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp
 10 20 25 (SEQ ID NO: 2)

wherein the carboxyl-terminus is an amide derivative, and/or Ala at position 2 is replaced with Pro, and/or Arg at position 8 is replaced with Lys,

15 the A and B chains being linked by disulphide bonds between A11-B10 and A24-B22 and wherein the human H3 relaxin analogue has relaxin bioactivity.

In accordance with a fourth aspect of the invention there is provided a composition comprising human H3 preprorelaxin or human H3 prorelaxin, having a signal, A chain, B
 20 chain and C chain in respect of human H3 preprorelaxin, and an A chain, B chain and C chain in respect of human H3 prorelaxin, the said amino acid chains having the amino acid sequences:

the A chain comprising:
 25
 Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser
 1 5 10 15
 Lys Ser Glu Ile Ser Ser Leu Cys
 30 20 (SEQ ID NO: 4)

the B chain comprising:

- 6 -

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
 1 5 10 15

5 Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp
 20 25 (SEQ ID NO: 2)

the signal sequence comprising:

10 Met Ala Arg Tyr Met Leu Leu Leu Leu Leu Ala Val Trp Val Leu Thr
 1 5 10 15

Gly Glu Leu Trp Pro Gly Ala Glu Ala
 20 25 (SEQ ID NO: 1)

15

and the C chain comprising:

Arg Arg Ser Asp Ile Leu Ala His Glu Ala Met Gly Asp Thr Phe Pro
 1 5 10 15

20

Asp Ala Asp Ala Asp Glu Asp Ser Leu Ala Gly Glu Leu Asp Glu Ala
 20 25 30

25

Met Gly Ser Ser Glu Trp Leu Ala Leu Thr Lys Ser Pro Gln Ala Phe
 35 40 45

Tyr Arg Gly Arg Pro Ser Trp Gln Gly Thr Pro Gly Val Leu Arg Gly
 50 55 60

30

Ser Arg
 65 (SEQ ID NO: 3)

In accordance with a fifth aspect of the invention, there is provided a composition comprising the C chain of human H3 relaxin, the C chain having the amino acid sequence:

35

- 16 -

B Chain

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
1 5 10 15

Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp
20 25

(SEO ID NO: 2)

the A and B chains being linked by disulphide bonds between A11-B10, A24-B22.

10

Human H3 relaxin possesses classical relaxin bioactivity. Human relaxins, H1 and H2 relaxin, bind to cells expressing relaxin receptors, such as THP-1 cells (Parsell et al (1996) *J. Biol. Chem.* 271, 27936-27941). H2 relaxin produces a dose dependent increase in cAMP production from these cells. Synthetic H3 relaxin produced according to this invention stimulated a dose dependent increase in cAMP in keeping with human H2 relaxin. The specificity of response in target cells bearing the human relaxin receptor as exhibited by H3 relaxin is demonstrated by the inability of bovine insulin (bINSL) or human insulin (hINSL3) to stimulate cAMP responses at doses up to 1 μ M in THP-1 cells.

20 The elicitation of a second messenger response (cAMP) by stimulating human relaxin receptors with human H3 relaxin, provides definitive evidence that human H3 relaxin has classic relaxin biological activity. Such assays in cells containing relaxin receptors, for example THP-1 cells as referred to above provides, a ready way to determine relaxin activity. In addition, the ability of human H3 relaxin to compete with P³²-labelled H2
25 relaxin in binding to relaxin binding sites in cells expressing relaxin receptors, again provides definitive confirmation of relaxin activity.

Other biological activities/assays for determining relaxin activity are known in the art. For example, bioassays used for the measurement of active relaxin during pregnancy and non-pregnancy, such as the guinea pig interpubic ligament assay may be used (Steinetz et al 30 (1960) *Endocrinology* 67, 102-115, and Sirosi et al (1983) *American Journal of Obstetrics and Gynaecology* 145: 402-405) may be used. Other bioassays include cAMP production

- 17 -

in THP-1 cells (Parsell *et al* (1996) J. Biol. Chem 271, 27936-27941).

Applicant has found that H3 relaxin analogues may be prepared where up to 9 amino acids are truncated from the N-terminus of the A chain, and up to 9 amino acids are truncated from the N-terminus of the B chain, and up to 5 amino acids are truncated from the C-terminus of the B chain.

The resulting relaxin analogues comprise a H3 relaxin A and B chain, the A chain having the amno acid sequence

10

Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser
1 5 10 15

Lys Ser Glu Ile Ser Ser Leu Cys

15

20

(SEQ ID NO: 4)

truncated by up to about 9 amino acids from amino-terminus,

and the B chain having the amino acid sequence:

20

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
1 5 10 15

Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp

25

20

25

(SEQ ID NO: 2)

truncated by up to 9 amino acids from the amino-terminus and/or up to about 5 amino acids from the carboxyl-terminus,

the A and B chains being linked by disulphide bonds between A11-B10 and A24-B22, and wherein the human H3 relaxin or analogue thereof has relaxin bioactivity. The A chain of human H3 relaxin contains an intrachain disulphide bond between Cys residues 10 and 15.

- 19 -

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
 1 5 10 15

Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp
 5 20 25 (SEQ ID NO: 2)

wherein the carboxyl-terminus is an amide derivative, and/or Ala at position 2 is replaced with Pro, and/or Arg at position 8 is replaced with Lys,

10 the A and B chains being linked by disulphide bonds between A11-B10 and A24-B22, and wherein the human H3 relaxin analogue has relaxin bioactivity.

The isolation, purification and characterisation of nucleic acid sequences encoding human H3 relaxin has allowed the characterisation and production of the signal sequence of
 15 human H3 relaxin, and the pro-sequence of human H3 relaxin.

The identification, purification and characterisation of the signal sequence and C chain of human H3 relaxin enables the prepro- and pro-human H3 relaxin to be produced.

20 In accordance with another aspect of the invention there is provided a composition comprising human H3 preprorelaxin or human H3 prorelaxin, having a signal, A chain, B chain and C chain in respect of human H3 preprorelaxin, and an A chain, B chain and C chain in respect of human H3 prorelaxin, the said amino acid chains having the amino acid sequences:

25 the A chain comprising:

Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser
 1 5 10 15

30 Lys Ser Glu Ile Ser Ser Leu Cys
 20 (SEQ ID NO: 4)

- 20 -

the B chain comprising:

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
 1 5 10 15
 5
 Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp
 20 25 (SEQ ID NO: 2)

the signal sequence comprising:

10
 Met Ala Arg Tyr Met Leu Leu Leu Leu Leu Ala Val Trp Val Leu Thr
 1 5 10 15
 Gly Glu Leu Trp Pro Gly Ala Glu Ala
 15 20 25 (SEQ ID NO: 1)

and the C chain comprising:

Arg Arg Ser Asp Ile Leu Ala His Glu Ala Met Gly Asp Thr Phe Pro
 20 1 5 10 15
 Asp Ala Asp Ala Asp Glu Asp Ser Leu Ala Gly Glu Leu Asp Glu Ala
 20 25 30
 25 Met Gly Ser Ser Glu Trp Leu Ala Leu Thr Lys Ser Pro Gln Ala Phe
 35 40 45
 Tyr Arg Gly Arg Pro Ser Trp Gln Gly Thr Pro Gly Val Leu Arg Gly
 51 55 60
 30
 Ser Arg
 65 (SEQ ID NO: 3)

In accordance with a further aspect of the invention there is provided the C chain of human
 35 H3 relaxin, said C chain having the amino acid sequence:

Fig. 1A

A: H3 relaxin assembled gene sequence

TATAAATGGGGGGCCAAGAGGCAGCAGAGACACTGGCCCACTCTCACGTTCAAAGCGTCT
CCGTCCAGCATGGCCAGGTACATGCTGCTGCTGCTCCTGGCGGTATGGGTGCTGACCGGG
M A R Y M L L L L L A V W V L T G
Signal peptide
GAGCTGTGGCCGGGAGCTGAGGCCCGGGCAGCGCCTTACGGGGTCAGGCTTTGCGGCCGA
E L W P G A E A R A A P Y G V R L C G R
GAATTCATCCGAGCAGTCATCTTCACCTGCGGGGGCTCCCGGTGGAGACGATCAGACATC
E F I R A V I F T C G G S R W R R S D I
B Chain
CTGGCCACGAGGCTATGG>gtgaggctggggagagagtggatgtagaaggggaacag-
L A H E A M

-----intron 2318bp-----
-cactaactctgttcacatcttttgcag<GAGATACCTTCCCGGATGCAGATGCTGATGAA
G D T F P D A D A D E

GACAGTCTGGCAGGCGAGCTGGATGAGGCCATGGGGTCCAGCGAGTGGCTGGCCCTGACC
D S L A G E L D E A M G S S E W L A L T
C Chain
AAGTCACCCAGGCCTTTTACAGGGGGCGACCCAGCTGGCAAGGAACCCCTGGGGTTCTT
K S P Q A F Y R G R P S W Q G T P G V L

CGGGGCAGCCGAGATGTCCTGGCTGGCCTTTCCAGCAGCTGCTGCAAGTGGGGGTGTAGC
R G S R D V L A G L S S S C C K W G C S
A Chain
AAAAGTGAAATCAGTAGCCTTTGCTAGTTTGAGGGCTGGGCAGCCGTGGGCACCAGGACC
K S E I S S L C *

AATGCCCCAGTCCTGCCATCCACTCAACTAGTGTCTGGCTGGGCACCTGTCTTTTCGAGCC
TCACACATTCAATTCATTCTACAAGTCACAGAGGCACTGTGGGCTCAGGCACAGTCTC
CCGACACCACCTATCCAACCCTGCCCTTTGACCAGCCTATCATGACCCTGGCCCCCTAAGG
AAGCTGTGCCCCCTGCCTGGTCAAGTGGGGACCCCCCATCCTGACCCCTGACCTCTCCCC
AGCCCTAACCATGCGTTTGCCTGGCCTACACACTCCACTGCCACAACCTGGGTCCCTACTC
TACCTAGGCTGGCCACACAGAGACCCCTGCCCCCTTCCAGTCCAAACTGTGGCCATTGT
CCCCTGACCAGCTAAAATCAAGCCTCTGTCTCAGTCCAGCCTTTGCACGCACGCTTCCTT
TGCCCTGCTTTCCATCCCCCTCTCCCTCCAACCTCCCCTGCCAGAGTTCCAAGGCTGTGGAC
CCCAGAGAAGGTGGCAGGTGGCCCCCCTAGGAGAGCTCTGGGCACATTGCAATCTTCCCA
AACTCCAATAATAAAATTGCAAGACTTTGGCAGAGAGTGTGTGTGTGTGTATGGTTG

Fig. 2A

A.

B Chain Aligns

	1	5	10	15	20	25
Human 1	KWKDDVIKLCGRELVRAQIAICGMSTWS					
Human 2	DSWMEEVIKLCGRELVRAQIAICGMSTWS					
Cons 1,2,3++LCGRE.+RA.I..CG.S.W.					
Human 3	RAAPYGVRLCGREFIRAVIFTCGGSRW					
Cons 3	R.APYGV+LCGREFIRAVIFTCGGSRW					
Mouse 3	RPAPYGVKLCGREFIRAVIFTCGGSRW					
Cons Mouse+++CGRE+.R.+I..CG.S..					
Mouse 1	RVSEEWMDGFIRMCGREYARELIKICGASVGRAL					

A Chain Aligns

	1	5	10	15	20
Human 1	RPYVALFEKCCLIGCTKRSLAKYC				
Human 2	QLYSALANKCCHVGCTKRSLARFC				
Cons 1,2,3	...+.L...CC..GC+K...+...C				
Human 3	DVLAGLSSSCCKWGCSKSEISSL				
Cons 3	DVLAGLSSSCC+WGCSKS+ISSLC				
Rat 3	DVLAGLSSSCCEWGCSKSQISSL				
Mouse 3	DVLAGLSSSCCEWGCSKSQISSL				
Cons Mouse	+.....S...CC..GCS+...I..L-C				
Mouse 1	ESGGLMSQQCCHVGCSRRSIKLYC				

SEQUENCE LISTING

<110> Howard Florey Institute of Experimental Physiology
and Medicine
5 University of Melbourne

<120> H3 Relaxin

<130> 7640120/PAS
10

<160> 10

<170> PatentIn version 3.0

15 <210> 1
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<212> PRT
<213> H3-signal

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1 5 10 15
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20 25

25 <210> 2
<211> 27
<212> PRT
<213> H3-B chain

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Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
1 5 10 15
Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp
35 20 25

<210> 3



PubMed

Nucleotide

Protein

Genome

Structure

PMC

Taxonomy

OMIM

Books

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History

Clipboard

Details

Display GenPept

Show 5

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Range: from begin

to end

Features: ☒ CDD

+

Refresh

☐ 1: Q8WXF3. Reports Relaxin-3 precurs...[gi:37999891]BLink, Conserved
Domains, Links

Comment Features Sequence

LOCUS Q8WXF3 142 aa linear PRI 20-FEB-2007

DEFINITION Relaxin-3 precursor (Prorelaxin H3) (Insulin-like peptide INSL7) (Insulin-like peptide 7) [Contains: Relaxin-3 B chain; Relaxin-3 A chain].

ACCESSION Q8WXF3

VERSION Q8WXF3 GI:37999891

DBSOURCE swissprot: locus REL3_HUMAN, accession [Q8WXF3](#); class: standard. extra accessions: Q6UXW5 created: Oct 10, 2003. sequence updated: Mar 1, 2002. annotation updated: Feb 20, 2007. xrefs: [AF447451.1](#), [AAL40345.1](#), [AB076563.1](#), [BAC53758.1](#), [AY358181.1](#), [AAQ88548.1](#), [2FHWA](#), [2FHWA](#) xrefs (non-sequence databases): UniGene:Hs.352155, Ensembl:ENSG00000171136, KEGG:hsa:117579, HGNC:17135, MIM: [606855](#), ArrayExpress:Q8WXF3, GermOnline:ENSG00000171136, RZPD-ProtExp:T3225, InterPro:IPR004825, SMART:SM00078, PROSITE:PS00262

KEYWORDS 3D-structure; Cleavage on pair of basic residues; Direct protein sequencing; Hormone; Signal.

SOURCE Homo sapiens (human)

ORGANISM [Homo sapiens](#)
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo.

REFERENCE 1 (residues 1 to 142)

AUTHORS Holloway, J.L., Lok, S. and Jaspers, S.R.

TITLE Direct Submission

JOURNAL Submitted (??-NOV-2001)

REMARK NUCLEOTIDE SEQUENCE [MRNA].

REFERENCE 2 (residues 1 to 142)

AUTHORS Kizawa, H., Nishi, K., Ishibashi, Y., Harada, M., Asano, T., Ito, Y., Suzuki, N., Hinuma, S., Fujisawa, Y., Onda, H., Nishimura, O. and Fujino, M.

TITLE Production of recombinant human relaxin 3 in AtT20 cells

JOURNAL Regul. Pept. 113 (1-3), 79-84 (2003)

PUBMED [12686464](#)

REMARK NUCLEOTIDE SEQUENCE [MRNA], AND PROTEIN SEQUENCE OF 26-34 AND 119-127.

REFERENCE 3 (residues 1 to 142)

AUTHORS Clark, H.F., Gurney, A.L., Abaya, E., Baker, K., Baldwin, D., Brush, J.,

Chen,J., Chow,B., Chui,C., Crowley,C., Currell,B., Deuel,B., Dowd,P., Eaton,D., Foster,J., Grimaldi,C., Gu,Q., Hass,P.E., Heldens,S., Huang,A., Kim,H.S., Klimowski,L., Jin,Y., Johnson,S., Lee,J., Lewis,L., Liao,D., Mark,M., Robbie,E., Sanchez,C., Schoenfeld,J., Seshagiri,S., Simmons,L., Singh,J., Smith,V., Stinson,J., Vagts,A., Vandlen,R., Watanabe,C., Wieand,D., Woods,K., Xie,M.H., Yansura,D., Yi,S., Yu,G., Yuan,J., Zhang,M., Zhang,Z., Goddard,A., Wood,W.I., Godowski,P. and Gray,A.

TITLE The secreted protein discovery initiative (SPDI), a large-scale effort to identify novel human secreted and transmembrane proteins: a bioinformatics assessment

JOURNAL Genome Res. 13 (10), 2265-2270 (2003)

PUBMED [12975309](#)

REMARK NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA].
Erratum:[Genome Res. 2003 Dec;13(12):2759]

REFERENCE 4 (residues 1 to 142)

AUTHORS Sudo,S., Kumagai,J., Nishi,S., Layfield,S., Ferraro,T., Bathgate,R.A. and Hsueh,A.J.

TITLE H3 relaxin is a specific ligand for LGR7 and activates the receptor by interacting with both the ectodomain and the exoloop 2

JOURNAL J. Biol. Chem. 278 (10), 7855-7862 (2003)

PUBMED [12506116](#)

REMARK INTERACTION WITH LGR7.

REFERENCE 5 (residues 1 to 142)

AUTHORS Liu,C., Eriste,E., Sutton,S., Chen,J., Roland,B., Kuei,C., Farmer,N., Jornvall,H., Sillard,R. and Lovenberg,T.W.

TITLE Identification of relaxin-3/INSL7 as an endogenous ligand for the orphan G-protein-coupled receptor GPCR135

JOURNAL J. Biol. Chem. 278 (50), 50754-50764 (2003)

PUBMED [14522968](#)

REMARK INTERACTION WITH GPCR135.

REFERENCE 6 (residues 1 to 142)

AUTHORS Liu,C., Chen,J., Sutton,S., Roland,B., Kuei,C., Farmer,N., Sillard,R. and Lovenberg,T.W.

TITLE Identification of relaxin-3/INSL7 as a ligand for GPCR142

JOURNAL J. Biol. Chem. 278 (50), 50765-50770 (2003)

PUBMED [14522967](#)

REMARK INTERACTION WITH GPCR142.

COMMENT [FUNCTION] May play a role in neuropeptide signaling processes. Ligand for LGR7, relaxin-3 receptor-1 (GPCR135) and relaxin-3 receptor-2 (GPCR142).
[SUBUNIT] Heterodimer of a B chain and an A chain linked by two disulfide bonds.
[SUBCELLULAR LOCATION] Secreted protein.
[SIMILARITY] Belongs to the insulin family.

FEATURES

source	Location/Qualifiers
	1..142
	/organism="Homo sapiens"
	/db_xref="taxon:9606"
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/experiment="experimental evidence, no additional details recorded"
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/note="Relaxin-3 B chain (By similarity).
/FTId=PRO_0000016082."

Region 29..32
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Region 33..>57
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/note="Insulin / insulin-like growth factor / relaxin family; insulin family of proteins; groups a number of active peptides which are evolutionary related including insulin, relaxin, insulin-like growth factors I and II, mammalian Leydig cell-specific insulin-like peptide (gene INSL3), and early placenta insulin-like peptide (ELIP) (gene INSL4), insect prothoracicotropic hormone (bombyxin), locust insulin-related peptide (LIRP), molluscan insulin-related peptides 1 to 5 (MIP), and C; cd00101"
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Bond bond(35,129)
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Region 37..47
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/locus_tag="UNQ6188/PRO20213"
/region_name="Helical region"
/experiment="experimental evidence, no additional details recorded"

Bond bond(47,142)
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/note="Interchain (between B and A chains) (By similarity)."

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121 lag1ssscck wgcsk1seiss lc

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//

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Feb 20 2007 16:53:14

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UniProtKB Entry

PIR View

UniProtKB Entry: **Q8WXF3**

ENTRY INFORMATION	
ENTRY NAME	REL3_HUMAN
ACCESSION NUMBERS	Q8WXF3; Q6UXW5
Integrated into Swiss-Prot on	2003-10-10
Sequence was last modified on	2002-03-01 (Sequence version 1)
Annotations were last modified on	2007-02-20 (Entry version 47)
NAME AND ORIGIN OF THE PROTEIN	
PROTEIN NAME	Relaxin-3 precursor
Synonyms	Prorelaxin H3 Insulin-like peptide INSL7 Insulin-like peptide 7
Contains	Relaxin-3 B chain Relaxin-3 A chain
GENE NAME	Name: RLN3 Synonym: INSL7; RXN3; ZINS4 ORF name: UNQ6188/PRO20213
SOURCE ORGANISM	Homo sapiens
TAXONOMY ID	9606 [NCBI, NEWT]
LINEAGE	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
REFERENCES	
[1]	Holloway JL; Lok S; Jaspers SR. Homo sapiens insulin homolog polypeptide. Submitted (NOV-2001) to EMBL/GenBank/DDBJ databases. <i>Position:</i> NUCLEOTIDE SEQUENCE [MRNA].
[2]	Kizawa H; Nishi K; Ishibashi Y; Harada M; Asano T; Ito Y et al. View Production of recombinant human relaxin 3 in AtT20 cells. 2003, <i>Regul. Pept.</i> , 113, 79-84.

	<i>Position:</i> NUCLEOTIDE SEQUENCE [MRNA]; PROTEIN SEQUENCE [MRNA] PubMed: 12686464; Medline: 22573778.
[3]	Clark HF; Gurney AL; Abaya E; Baker K; Baldwin DT; Brush J et al. The secreted protein discovery initiative (SPDI), a large-scale effort to identify human secreted and transmembrane proteins: a bioinformatics assessment. 2003, <i>Genome Res.</i> , 13, 2265-2270. <i>Position:</i> NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA]. PubMed: 12975309; Medline: 22887296.
[4]	Sudo S; Kumagai J; Nishi S; Layfield S; Ferraro T; Bathgate RAD et al. H3 relaxin is a specific ligand for LGR7 and activates the receptor and the exoloop 2. 2003, <i>J. Biol. Chem.</i> , 278, 7855-7862. <i>Position:</i> INTERACTION WITH LGR7. PubMed: 12506116; Medline: 22499664.
[5]	Liu C; Eriste E; Sutton S; Chen J; Roland B; Kuei C et al. View all . Identification of relaxin-3/INSL7 as an endogenous ligand for the GPCR135. 2003, <i>J. Biol. Chem.</i> , 278, 50754-50764. <i>Position:</i> INTERACTION WITH GPCR135. PubMed: 14522968;
[6]	Liu C; Chen J; Sutton S; Roland B; Kuei C; Farmer N et al. View all . Identification of relaxin-3/INSL7 as a ligand for GPCR142. 2003, <i>J. Biol. Chem.</i> , 278, 50765-50770. <i>Position:</i> INTERACTION WITH GPCR142. PubMed: 14522967;

COMMENTS

FUNCTION	May play a role in neuropeptide signaling processes. Ligand for LGR7 relaxin-3 receptor-2 (GPCR142).
SUBUNIT	Heterodimer of a B chain and an A chain linked by two disulfide bonds.
SUBCELLULAR LOCATION	Secreted protein.
SIMILARITY	Belongs to the insulin family.

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DATABASE CROSS-REFERENCES

ARRAYEXPRESS	Q8WXF3.
EMBL	AF447451,AAL40345.1,mRNA. [GenBank, DDBJ] AB076563,BAC53758.1,mRNA. [GenBank, DDBJ] AY358181,AAQ88548.1,ALT_INIT,mRNA. [GenBank, DDBJ]
ENSEMBL	ENSG00000171136,Homo sapiens.
GERMONLINE	ENSG00000171136,Homo sapiens
HGNC	HGNC:17135,RLN3.
INTERPRO	IPR004825,Ins/IGF/relax.

KEGG	hsa:117579.
MIM	606855, gene.
PDB	2FHW, NMR, A=119-142, B=26-52.
PROSITE	PS00262, INSULIN, 1.
RZPD_PROTEXP	T3225
SMART	SM00078, IIGF, 1.
UNIGENE	Hs.352155
UniRef	View cluster of proteins with at least 50% / 90% / 100% identity.

KEYWORDS

3D-structure; Cleavage on pair of basic residues; Direct protein sequencing; Hormone; Signal

FEATURES

Feature	Description
SIGNAL PEPTIDE	
PEPTIDE	Relaxin-3 B chain (By similarity). /FTId=PRO_00000
PROPEPTIDE	Connecting peptide (BY SIMILARITY) /FTId=PRO_00000
PEPTIDE	Relaxin-3 A chain (By similarity). /FTId=PRO_00000
DISULFIDE BOND	Interchain (between B and A chains) (BY SIMILARITY
DISULFIDE BOND	Interchain (between B and A chains) (BY SIMILARITY
DISULFIDE BOND	BY SIMILARITY
STRAND	
TURN	
HELIX	
TURN	
HELIX	
TURN	
HELIX	
TURN	

Feature sequence (Put the mouse on the feature above to see the sequence below):

RAAPYGVRLCGREFIRAVIFTCGGSRW

SEQUENCE

LENGTH	142 aa
MOLECULAR WEIGHT	15451 Da
CRC64 CHECKSUM	23A3E095034B31E4

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for Q8WXF3

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UniProtKB/Swiss-Prot entry Q8WXF3

[\[Entry info\]](#) [\[Name and origin\]](#) [\[References\]](#) [\[Comments\]](#) [\[Cross-references\]](#)
[\[Keywords\]](#) [\[Features\]](#) [\[Sequence\]](#) [\[Tools\]](#)

Note: most headings are clickable, even if they don't appear as links. They link to the user manual or other documents.

Entry information

Entry name	REL3_HUMAN
Primary accession number	Q8WXF3
Secondary accession number	Q6UXW5
Integrated into Swiss-Prot on	October 10, 2003
Sequence was last modified on	March 1, 2002 (Sequence version 1)
Annotations were last modified on	February 20, 2007 (Entry version 47)

Name and origin of the protein

Protein name	Relaxin-3 [Precursor]
Synonyms	Prorelaxin H3 Insulin-like peptide INSL7 Insulin-like peptide 7

Contains

Relaxin-3 B chain
Relaxin-3 A chain

Gene name

Name: RLN3
Synonyms: INSL7, RXN3, ZINS4
ORFNames: UNQ6188/PRO20213

From

Taxonomy

Homo sapiens (Human) [TaxID: 9606]
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata;
Euteleostomi; Mammalia; Eutheria; Euarchontoglires;
Primates; Haplorrhini; Catarrhini; Hominidae; Homo.

References

[1] NUCLEOTIDE SEQUENCE [MRNA].

Holloway J.L., Lok S., Jaspers S.R.;
"Homo sapiens insulin homolog polypeptide."
Submitted (NOV-2001) to the EMBL/GenBank/DDBJ databases.

[2] NUCLEOTIDE SEQUENCE [MRNA], AND PROTEIN SEQUENCE OF 26-34 AND 119-12 DOI=10.1016/S0167-0115(02)00304-X; PubMed=12686464 [NCBI, ExPASy, EBI, Israel, .


Kizawa H., Nishi K., Ishibashi Y., Harada M., Asano T., Ito Y., Suzuki N., Hinuma S., Fujis Y., Onda H., Nishimura O., Fujino M.;

"Production of recombinant human relaxin 3 in AtT20 cells.";

Regul. Pept. 113:79-84(2003).

[3] NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA].

DOI=10.1101/gr.1293003; PubMed=12975309 [NCBI, ExPASy, EBI, Israel, Japan]

Clark H.F., Gurney A.L., Abaya E., Baker K., Baldwin D.T., Brush J., Chen J., Chow B., Cl Crowley C., Currell B., Deuel B., Dowd P., Eaton D., Foster J.S., Grimaldi C., Gu Q., Hass Heldens S., , Gray A.M.;

"The secreted protein discovery initiative (SPDI), a large-scale effort to identify novel human secreted and transmembrane proteins: a bioinformatics assessment.";

Genome Res. 13:2265-2270(2003).

[4] INTERACTION WITH LGR7.

DOI=10.1074/jbc.M212457200; PubMed=12506116 [NCBI, ExPASy, EBI, Israel, Japan]

Sudo S., Kumagai J., Nishi S., Layfield S., Ferraro T., Bathgate R.A.D., Hsueh A.J.W.;

"H3 relaxin is a specific ligand for LGR7 and activates the receptor by interacting with both ectodomain and the exoloop 2.";

J. Biol. Chem. 278:7855-7862(2003).

[5] INTERACTION WITH GPCR135.

DOI=10.1074/jbc.M308995200; PubMed=14522968 [NCBI, ExPASy, EBI, Israel, Japan]

Liu C., Eriste E., Sutton S., Chen J., Roland B., Kuei C., Farmer N., Joernvall H., Sillard R Lovenberg T.W.;

"Identification of relaxin-3/INSL7 as an endogenous ligand for the orphan G-protein coupled receptor GPCR135.";

J. Biol. Chem. 278:50754-50764(2003).

[6] INTERACTION WITH GPCR142.

DOI=10.1074/jbc.M308996200; PubMed=14522967 [NCBI, ExPASy, EBI, Israel, Japan]

Liu C., Chen J., Sutton S., Roland B., Kuei C., Farmer N., Sillard R., Lovenberg T.W.;

"Identification of relaxin-3/INSL7 as a ligand for GPCR142.";

J. Biol. Chem. 278:50765-50770(2003).

Comments

- **FUNCTION:** May play a role in neuropeptide signaling processes. Ligand for LGR7, relaxin-3 receptor-1 (GPCR135) and relaxin-3 receptor-2 (GPCR142).
- **SUBUNIT:** Heterodimer of a B chain and an A chain linked by two disulfide bonds.
- **SUBCELLULAR LOCATION:** Secreted protein.
- **SIMILARITY:** Belongs to the insulin family.

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Cross-references

Sequence databases

EMBL	AF447451; AAL40345.1; -; mRNA.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	AB076563; BAC53758.1; -; mRNA.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	AY358181; AAQ88548.1; ALT_INIT; mRNA.	[EMBL / GenBank / DDBJ] [CoDingSequence]

UniGene Hs.352155

3D structure databases

PDB 2FWH; NMR; A=119-142, B=26-52.[ExPASy / RCSB / EBI]

ModBase Q8WXF3.

Organism-specific gene databases

HGNC HGNC:17135; RLN3.

GeneCards RLN3.

GeneLynx RLN3; Homo sapiens.

GenAtlas RLN3.

MIM 606855; gene. [NCBI / EBI]

HOVERGEN [Family / Alignment / Tree]

Gene expression databases

CleanEx HGNC:17135; RLN3.

ArrayExpress Q8WXF3; -.

GermOnline ENSG00000171136; Homo sapiens.

Family and domain databases

InterPro IPR004825; Ins/IGF/relax.
Graphical view of domain structure.

SMART SM00078; IIGF; 1.
SMART graphical view of domain structure.

PROSITE PS00262; INSULIN; 1.

ProDom [Domain structure / List of seq. sharing at least 1 domain]

BLOCKS Q8WXF3.

Genome annotation databases

Ensembl ENSG00000171136; Homo sapiens. [Contig view]

KEGG hsa:117579; -.

Other

RZPD-
ProtExp Clones: T3225

SOURCE RLN3; Homo sapiens.

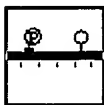
ProtoNet Q8WXF3.

UniRef View cluster of proteins with at least 50% / 90% / 100% identity.

Keywords

3D-structure; Cleavage on pair of basic residues; Direct protein sequencing; Hormone Signal.

Features



Feature table viewer



Feature aligner

Key	From	To	Length	Description	FTId
SIGNAL	1	25	25		
PEPTIDE	26	52	27	Relaxin-3 B chain (<i>By similarity</i>).	PRO_000C
PROPEP	55	118	64	Connecting peptide (<i>By similarity</i>).	PRO_000C

PEPTIDE	119	142	24	Relaxin-3 A chain (<i>By similarity</i>).	PRO_000C
DISULFID	35	129		Interchain (between B and A chains) (<i>By similarity</i>).	
DISULFID	47	142		Interchain (between B and A chains) (<i>By similarity</i>).	
DISULFID	128	133		By similarity.	
STRAND	29	32	4		
TURN	36	36	1		
HELIX	37	47	11		
TURN	48	48	1		
HELIX	120	130	11		
TURN	131	131	1		
HELIX	135	139	5		
TURN	140	141	2		

Sequence information

Length: **142 AA** [This is the length of the unprocessed precursor]

Molecular weight: **15451 Da** [This is the MW of the unprocessed precursor]

CRC64: **23A3E095034B31E** is a checksum on the sequence

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      130          140
LAGLSSSCCK WGCSKSEISS LC

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Q1
in
F/
foi

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or at NCBI (USA)



Sequence analysis tools: ProtParam,
ProtScale, Compute pI/Mw, PeptideMass,
PeptideCutter, Dotlet (Java)



ScanProsite, MotifScan



Submit a homology modeling request to
SWISS-MODEL



NPSA Sequence
analysis tools



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for Q8WXF3

UniProtKB/Swiss-Prot: Q8WXF3 (REL3_HUMAN)

The section of the sequence Q8WXF3 (REL3_HUMAN) you have selected corresponds to:

PEPTIDE 26 52 Relaxin-3 B chain (By similarity).
/FTid=PRO_0000016082.

In one-letter code:

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61 EAMGDTFPDA	DADEDSLAGE	LDEAMGSSEW	LALTKSPQAF	YRGRPSWQGT	PGVLRGSI
121 LAGLSSSCCK	WGCSKSEISS	LC			

In three-letter code:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1 Met	Ala	Arg	Tyr	Met	Leu	Leu	Leu	Leu	Leu	Ala	Val	Trp	Val	Leu
16 Thr	Gly	Glu	Leu	Trp	Pro	Gly	Ala	Glu	Ala	Arg	Ala	Ala	Pro	Tyr
31 Gly	Val	Arg	Leu	Cys	Gly	Arg	Glu	Phe	Ile	Arg	Ala	Val	Ile	Phe
46 Thr	Cys	Gly	Gly	Ser	Arg	Trp	Arg	Arg	Ser	Asp	Ile	Leu	Ala	His
61 Glu	Ala	Met	Gly	Asp	Thr	Phe	Pro	Asp	Ala	Asp	Ala	Asp	Glu	Asp
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91 Leu	Ala	Leu	Thr	Lys	Ser	Pro	Gln	Ala	Phe	Tyr	Arg	Gly	Arg	Pro
106 Ser	Trp	Gln	Gly	Thr	Pro	Gly	Val	Leu	Arg	Gly	Ser	Arg	Asp	Val
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136 Ser	Glu	Ile	Ser	Ser	Leu	Cys								

Direct similarity search submission of this **subsequence** to

BLAST

BLAST submission on
ExPASy/SIB
or at NCBI (USA)



Sequence analysis tools: ProtParam,
ProtScale, Compute pI/Mw, PeptideMass,
PeptideCutter, Dotlet (Java)



ScanProsite



Direct Submission to SWISS-MODEL

NPS@ NPSA Sequence
analysis tools



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SEQUENCE LISTING

<110> Del Borgo, Mark
 Wade, John D.
 Bathgate, Ross D.
 Hughes, Richard A.
 Howard Florey Institute of Physiology and Medicine
 The University of Melbourne

<120> Relaxin Superfamily Peptide Analogues

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<223> relaxin-1 a-chain

<400> 16

Arg Pro Tyr Val Ala Leu Phe Glu Lys Cys Cys Leu Ile Gly Cys Thr
1 5 10 15

Lys Arg Ser Leu Ala Lys Tyr Cys
20

<210> 17

<211> 24

<212> PRT

<213> Homo sapiens

<220>

<223> relaxin-2 a-chain

<400> 17

Gln Leu Tyr Ser Ala Leu Ala Asn Lys Cys Cys His Val Gly Cys Thr
1 5 10 15

Lys Arg Ser Leu Ala Arg Phe Cys
20

<210> 18

<211> 24

<212> PRT

<213> Homo sapiens

<220>

<223> relaxin-3 a-chain

<400> 18

Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser
1 5 10 15

Lys Ser Glu Ile Ser Ser Leu Cys
20

<210> 19

<211> 26

<212> PRT

<213> Homo sapiens

<220>

<223> insulin a-chain

<400> 19

Ser Leu Gln Lys Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
1 5 10 15

Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
20 25

<210> 20
 <211> 25
 <212> PRT
 <213> Homo sapiens

<220>
 <223> insulin-like growth factor 1 (IGF-1) a-chain

<400> 20
 Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys Asp
 1 5 10 15
 Leu Arg Arg Leu Glu Met Tyr Cys Ala
 20 25

<210> 21
 <211> 25
 <212> PRT
 <213> Homo sapiens

<220>
 <223> insulin-like growth factor 2 (IGF-2) a-chain

<400> 21
 Arg Arg Ser Arg Gly Ile Val Glu Glu Cys Cys Phe Arg Ser Cys Asp
 1 5 10 15
 Leu Ala Leu Leu Glu Thr Leu Cys Ala
 20 25

<210> 22
 <211> 26
 <212> PRT
 <213> Homo sapiens

<220>
 <223> insulin-like 3 (INSL3) a-chain (Leydig
 insulin-like (Ley I-L)/relaxin like factor (RLF))

<400> 22
 Ala Ala Ala Thr Asn Pro Ala Arg Tyr Cys Cys Leu Ser Gly Cys Thr
 1 5 10 15
 Gln Gln Asp Leu Leu Thr Leu Cys Pro Tyr
 20 25

<210> 23
 <211> 25
 <212> PRT
 <213> Homo sapiens

<220>
 <223> insulin-like 4 (INSL4) a-chain (placentin/early
 placenta insulin-like (EPIL))

<400> 23

Arg Ser Gly Arg His Arg Phe Asp Pro Phe Cys Cys Glu Val Ile Cys
 1 5 10 15

Asp Asp Gly Thr Ser Val Lys Leu Cys
 20 25

<210> 24

<211> 24

<212> PRT

<213> Homo sapiens

<220>

<223> insulin-like 5 (INSL5) a-chain

<400> 24

Met Ser Arg Gln Asp Leu Gln Thr Leu Cys Cys Thr Asp Gly Cys Ser
 1 5 10 15

Met Thr Asp Leu Ser Ala Leu Cys
 20

<210> 25

<211> 24

<212> PRT

<213> Homo sapiens

<220>

<223> insulin-like 6 (INSL6) a-chain

<400> 25

Arg Lys Arg Arg Gly Tyr Ser Glu Lys Cys Cys Leu Thr Gly Cys Thr
 1 5 10 15

Lys Glu Glu Leu Ser Ile Ala Cys
 20